Medical Therapy of Atrial Fibrillation: What’s New

Ralph Augostini, MD FACC FHRS
Learning Objectives

- Review the growing incidence and importance of AF in the population
- Summarize pharmacologic options for AF management
- Discuss the use of anticoagulation in AF for stroke prevention
- Discuss new therapies introduced over the past year
Guidelines


- 2011 ACCF/AHA/HRS Focused Update on the Management of Patients with Atrial Fibrillation. (Updating the 2006 Guidelines)

- 2011 ACCF/AHA/HRS Focused Update on the Management of Patients with Atrial Fibrillation (Update on Dabigatran)
Atrial Fibrillation

- Most common sustained disturbance in heart rhythm.
- Affects over 2 million adults in the US.

- Associated with 5 fold increase in stroke.
  - Contributing factor for stroke recurrence and severity.

- Hospitalizations for AF have increased 2-3 fold in recent years.

- Public health burden is enormous and expected to increase over the next decades.


Projected Number of Adults With AF in the US: 1995 to 2050.

Mechanism of Atrial Fibrillation

- 1959 Moe theorized that AF resulted from multiple wavelets of reentry propagating randomly throughout the atria.

- Requires a trigger and the substrate capable of maintaining atrial fibrillation.

- 90% of triggers originate in the pulmonary veins
Etiology of atrial fibrillation

- AF is associated with almost any type of underlying heart disease that causes changes in the atrial myocardium including distension, inflammation, hypertrophy, ischemia, fibrosis and infiltration.

- Normal age-related changes like infiltration and fibrosis
  - <1% in adults younger than age 55
  - After age 75 increases to 11%.

- Autonomic nervous system inputs altering atrial electrophysiologic properties.

- In up to 15% of cases, no structural heart disease and no identifiable cause for the arrhythmia.
General Approach to the Patient with Atrial Fibrillation

- Establish an Accurate Diagnosis of AF
  - May require temporarily inhibiting pacing
  - Distinguish from other SVTs, MAT, A Flutter
Atrial Fibrillation
Multifocal Atrial Tachycardia
Atrial Flutter
Classification of Atrial Fibrillation

- **Paroxysmal**
  - Recurrent AF, > 2 episodes that terminate spontaneously within 7 days.

- **Persistent**
  - AF sustained beyond 7 days or lasting < 7 days but requires electrical or pharmacologic cardio version

- **Longstanding Persistent**
  - Continuous AF, > 1 year duration

- **Permanent**
  - Cardio version failed or not attempted. Decision made not to pursue restoration of sinus rhythm by any means.
  - *Not appropriate for curative ablation.*
APPROACHES TO AF THERAPY

Rate control plus anticoagulation preferred

- No or lesser AF symptoms
- More SHD
- Toxicity Risk
- Elderly
- Greater risk of proarrhythmia

Rhythm control preferred

- Greater AF symptoms
- Symptoms despite rate control
- Younger age
- No or lesser SHD
- Rx option of class IC AAD

In anticoagulation candidates, continue anticoagulation indefinitely
General Approach to the Patient with Atrial Fibrillation

- Determine Symptoms, Clinical History and AF Pattern
  - Onset
  - Presence/nature of symptoms
  - Type

- Exclude Structural Heart Disease
  - Help individualize treatment
  - Rule out CAD

- Identify Correctable Secondary Causes
  - Hyperthyroidism, Sleep Apnea, ETOH, etc.

- Develop a Treatment Strategy
DIAGNOSTIC WORKUP

- **Minimum Evaluation**
  - History and physical – Symptoms with AF, CV disease
  - Electrocardiogram – LVH, MI, BBB, WPW
  - Echocardiogram – LVH, LAE, EF, Valve Disease
  - Labs – TSH, Renal function, LFTs

- **Additional Testing**
  - ETT – CAD, Exercise induced SVT / AF
  - Holter / Event Monitor – Confirm AF and Symptoms
  - TEE – LA clot
  - EPS – SVT triggered AF
  - Sleep Study

AHA / ACC / ECS Guidelines
Management Principles

- **Cornerstones of AF Management**
  - Rate Control, Rhythm Control, Prevention of Thromboembolism

- **Goals of Therapy**
  - Symptom control, stroke prevention, reduction of hospitalizations.

- **Reversible causes do not require long term treatment.**

- **Continued symptoms or difficult management.**
  - Consult Electrophysiology
Rate vs Rhythm Control

- AFFIRM, RACE and AF CHF trials have shown no mortality benefit to a rhythm control strategy compared with rate control.

- Rate control without attempts at restoration or maintenance of SR is reasonable in patients who are asymptomatic and elderly.

- Restoration and maintenance of SR is a reasonable approach.
Stroke Prevention

- Anti-thrombotic therapy is recommended for all patients regardless of rate vs. rhythm control except in lone AF or contraindications.
Rate Control Strategy

- Adequate control of Ventricular Response
  - Control symptoms (mean <110bpm)
  - Prevent tachycardia-mediated cardiomyopathy
  - Atrial Flutter is more difficult to rate control
Rate Control Guidelines

AFFIRM

Average HR up to 80 bpm at rest and either an average rate up to 100 bpm during Holter monitoring with no rate above 100% of maximum age adjusted predicted exercise HR or max HR of 110 bpm during 6 min walk test.

RACE

< 100 bpm at rest.

2011 update to the 2006 AF guidelines

Strict control not beneficial compared to achieving a resting HR < 110 bpm in patients with asymptomatic persistent AF with stable LV function (EF >40%)

Uncontrolled tachycardia over time is associated with reduction in ventricular performance.
Medications to Control Ventricular Response

- AV Nodal blocking drugs can be used to control the ventricular response
  - **Beta-blockers**
    - The most effective for rate control
    - May not be tolerated in severe lung disease
  - **Esmolol**
    - IV 500mcg/kg, then 50-200 mcg/kg/min.
  - **Metoprolol**
    - IV 2.5-5mg over 2 mins up to 3 doses
    - P.O 25-100mg bid, 25mg -200mg daily (XL)
  - **Atenolol**
    - P.O 25-100mg daily
  - **Carvedilol**
    - P.O. 3.125 – 25mg Q12hrs up to 50mg Q12hrs for pt >85kg.
    - CR 10-80mg daily
Medications for Rate Control

- **Calcium Channel Blockers** (non-dihydropyridine)
  - Negative inotrope
  - Avoid in patients with reduced LV function.

- **Diltiazem**
  - IV 0.25mg/kg (average 20mg) over 2 mins, 2nd bolus can be given if HR > 100 bpm, then 5-15mg/hr.
  - P.O. 120-480mg daily (slow release preferred)

- **Verapamil**
  - IV 0.075 -0.15mg/kg over 2 mins (2.5-10mg IV x1, Max 20mg)
  - P.O. 120 – 480mg daily (slow release preferred)
Medications for Rate Control

- **Digoxin**
  - Helpful for resting tachycardia but provides relatively poor rate control during exertion.
  - Useful in patients with systolic heart failure
  - IV 0.25 mg Q 2 hrs (up to 1.5 mg), then 0.125 – 0.375 mg daily.
  - P.O. 0.125 – 0.375 mg daily.
“Ablate and Pace”

Implantation of pacemaker, followed by complete AV Node ablation.

- Does not eliminate AF.
- Goal is to achieve controlled, regular heart rate.
- Best for chronic AF not amenable to curative RFA, poorly tolerated or unsuccessful medical treatment.
- Requires life-long anticoagulation.
Cardioversion

- May be achieved by drug or electrical shock.
- DCCV more effective than pharmacological cardio version.
- Pharmacologic cardio version is more effective with recent the onset of AF.
- The risk of thromboembolism is the same with either approach.
- Be prepared for significant bradycardia after cardio version in patients on high dose AV nodal blocking drugs.
Cardioversion

- Synchronized
- Contraindications
  - Hypokalemia
  - Dig toxicity
  - Intracardiac thrombus
- If onset of AF > 48 hours
  - TEE to R/O left atrial thrombus
  - At least 4 weeks of therapeutic INRs
Maintenance of Sinus Rhythm in Specific Patient Populations
Suggested Scheme Including Dronedarone

No (or minimal) Heart Disease
- Flecainide
- Propafenone
- Sotalol
- Dronedarone
  - Amiodarone
  - Dofetilide
  - Catheter Ablation

Hypertension
- Substantial LVH
  - No
    - Flecainide
    - Propafenone
    - Sotalol
    - Dronedarone
      - Amiodarone
      - Dofetilide
      - Catheter Ablation
  - Yes
    - Amiodarone
    - Dronedarone
      - Catheter Ablation

Coronary Artery Disease
- Dofetilide
- Sotalol
- Dronedarone
  - Amiodarone
  - Catheter Ablation

Heart Failure
- Amiodarone
- Dofetilide
  - Catheter Ablation

Antiarrhythmic Drug Therapy

- Indicated for symptomatic PAF or recurrent AF after cardio version.

- Recurrence of AF on drug is not indicative of failure.

- A specific drug should be abandoned if there is no symptomatic improvement or causes adverse effects.
Rhythm Control
Antiarrhythmic Drug Therapy

- Drug choice based on side effect profile, presence/absence of structural heart disease, heart failure and hypertension.

- Individualized and accounts for underlying renal and hepatic function.
Initiating Antiarrhythmic Drug Therapy

- Ensure normal electrolytes
  - Potassium 4.0
  - Magnesium 2.0
- Determine renal function
- Baseline ECG parameters
- Ensure adequate anticoagulation
  - Therapeutic INR for 4 consecutive weeks
  - TEE, no evidence LA or LAA thrombus
Class IC Agents

- Strong Na Channel blocker
- Depress Phase 0
- Slow conduction
- Little effect on repolarization
- May accelerate AV conduction in AF / AFL (1:1 conduction)
  - Control rate first with AV blocking agents
- Use Dependency
  - ETT after loading
- Do not use in structural heart disease
- May be initiated outpatient in patients with PAF, in NSR at the time. Class Ila

Monophasic Action Potential
(Cardiac Muscle Cell)
Class IC Agents

FLECAINIDE (TAMBOCOR)
- 50 - 150mg Q 12 hrs
- Side Effects
  - Dizziness
  - Visual disturbances
  - Ventricular proarrhythmia
- ETT after 4 doses

PROPAFENONE (RYTHMOL)
- 150 – 300mg Q 8 hrs
- 225 – 425mg Q 12 hrs (SR)
- Side Effects
  - Dizziness
  - Taste disturbance
  - GI complaints
  - Ventricular proarrhythmia
- ETT after 5 doses of IR.
Class III Agents

- Potassium channel blockers
- Delay repolarization (Phase 3)
- Increase action potential duration and ERP
- Shows in QT interval prolongation
- All require close follow up.
  *AAD Clinic*
Sotolol (Betapace)

- P.O. 80 -160 mg Q 12 hours
- Dose based on renal function
- Hospitalize for initiation
- Monitor QT interval for at least 5 doses.
  - QT not to exceed 500ms
- Also has class II activity.
  - Consider stopping other beta-blockers
- Side effects
  - Pro-arrhythmia, Torsade de Pointes
  - QT prolongation
  - Bradycardia
  - fatigue
**Dofetilide (Tikosyn)**

- Very selective potassium channel blocker
- High risk for torsade
- Initiate in Hospital
- Many drug contraindications.
- Side Effects
  - QT prolongation
  - Torsade de Pointes
- Dose 125 – 500mcg Q 12 hours
- Based on renal function
- Restricted to trained prescribers
- QTc<440ms prior to initiation, then no greater 500ms
Drug-Induced Pro-arrhythmia – Torsades
Dronedarone (Multaq)

- Structurally similar to Amiodarone
- Shorter elimination half life
- Class I, II and IV actions as well
- Contra-indicated in severe or recently decompensated heart failure
- May cause severe liver injury
- Monitor QTc and serum Cr

- Dose 400mg PO BID
- Can be initiated as outpatient
- Side Effects
  - New or worsening CHF
  - Bradycardia
  - QT prolongation
  - Hepatotoxicity
  - Elevated serum Cr
Current monitoring protocol in the Anti-arrhythmic clinic

- Follow-up: every 6 months except as noted
  - ECG (VR, PR, QT/QTc)
  - TFTs
  - LFTs, monthly X 6, 9 mo, 12 mo
  - Renal function, at one month, then every 6 m
  - Electrolytes (K, Mg)
  - Vitals
  - If no echo or assessment of LV function completed, or if LVEF less than 50%: refer back to prescriber (recent addition)
Initial experience

- Increases in serum creatinine were common (~40%), and could be significant.
- Onset of changes in serum creatinine was variable
- Common ADE: GI (24%); Asthenia (18%), worsening HF (6%)
FDA Safety Bulletins
(New signals in Adverse event reporting system)

- January 2011: Hepatotoxicity/failure
- March 2011: Renal impairment/failure
  - Relabeling on drug interactions (warfarin)
- June 2011: Pulmonary Toxicity (Post-marketing cases of interstitial lung disease including pneumonitis and pulmonary fibrosis)
- July 2011: Increased risk of CV event or death in patients with permanent AF
EMA recommends restricting use of dronedarone:

- patients currently taking Multaq “have their treatment evaluated by their doctor at their next scheduled appointment.”

- “increased risk of Multaq causing injury to the liver as well as the lungs when used in accordance with the currently approved prescribing information”
According to the EMA's Committee for Medicinal Products for Human Use (CHMP), Multaq (dronedarone)]:

should be restricted to patients with paroxysmal or persistent atrial fibrillation when sinus rhythm is obtained and should not be used when atrial fibrillation is still present.

It should not be used in permanent atrial fibrillation or in patients with heart failure or those with left ventricular systolic dysfunction.

It should also not be used in patients with a previous lung or liver injury following treatment with amiodarone.

Patients with nonpermanent atrial fibrillation treated with dronedarone should be monitored by a specialist and have their lung, liver, and heart-rhythm function checked regularly.
Amiodarone

- Most effective, but associated with relatively high toxicity.
  - Toxicity is dose related.
  - Not usually first line choice.
  - Can be initiated on outpatient basis

- Has Class I, II, and IV actions as well
  - Bradycardia, AV block
  - May need to reduce beta-blocker or calcium channel blocker dose.
  - Digoxin dose, reduce by half.

- IV 150mg over 10 mins, then 0.5 -1 mg/min

- P.O. Loading dose 800mg daily x 1 week, 600mg daily x 1 week, 400mg daily for 4-6 weeks, then 200mg daily.

Practical Rate and Rhythm management of Atrial Fibrillation. January 2010
Amiodarone

- Side effects
  - GI
  - Photosensitivity
  - Pulmonary Fibrosis
  - Thyroid Dysfunction
  - Hepatic Dysfunction
  - Ophthalmologic issues
  - Tremors, coordination issues.

- Drug interactions
  - Warfarin
  - Statins

- Ongoing surveillance
  - CXR
  - PFTs with DLCO
  - TFTs
  - LFTs
Amiodarone Photosensitivity
Stroke Prevention

- Anti-thrombotic therapy is recommended based on CHADS2 score, except in patients with lone AF or contraindications to Warfarin.

- Patients with AF and hypertrophic cardiomyopathy, mitral stenosis or a mechanical valve should be treated with Warfarin.

- Recommendations are the same for patients with atrial flutter.
## Risk Factors for Thromboembolism in AF

<table>
<thead>
<tr>
<th>High-Risk Factors</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous CVA / TIA / Embolism</td>
<td>High-risk factor or ≥ 2 moderate-risk factors</td>
</tr>
<tr>
<td>Mitral Stenosis</td>
<td>Coumadin INR 2-3 (mechanical valve INR &gt; 2.5)</td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate-Risk Factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 75 yrs</td>
<td>1 moderate-risk factor</td>
</tr>
<tr>
<td>HTN</td>
<td>ASA or Coumadin</td>
</tr>
<tr>
<td>CHF</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td></td>
</tr>
<tr>
<td>EF &lt; 35%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weaker-Risk Factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1 Weak or no risk factor</td>
</tr>
<tr>
<td>CAD</td>
<td>ASA 81-325mg daily</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td></td>
</tr>
<tr>
<td>Age 65 – 74 yrs</td>
<td></td>
</tr>
</tbody>
</table>

AHA / ACC / ECS Guidelines 2006
What is a chads score?

Scoring system used to risk stratify patients with nonvalvular AF to determine the need for warfarin.

Annual risk of stroke
Score 0 = 1.9%
Score 6 = 18.2%

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; criteria</th>
<th>Points</th>
<th>Stroke risk score</th>
<th>Recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stroke or TIA</td>
<td>2</td>
<td>High</td>
<td>Warfarin (INR 2–3)</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>Moderate</td>
<td>Warfarin or aspirin</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td></td>
<td>Aspirin 100–300 mg daily</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>
Warfarin (Coumadin)

- Inhibits vitamin K – dependent coagulation factor synthesis
- P.O. 2-10 mg daily
- Requires ongoing monitoring
- Goal INR 2.0 – 3.0
- Risk of major bleeding
- Multiple drug interactions
What about ASA + Plavix?

- Aspirin and Clopidogrel - not a substitute for warfarin.

- May be considered to reduce risk of major vascular events in patients who are poor candidates for warfarin. Class IIb

- ACTIVE-A trial – combination was more effective than ASA alone in preventing strokes in high risk patients not suitable for warfarin, but caused more major bleeding than ASA alone.
Dabigatran (Pradaxa)

- Approved for the prevention of stroke and systemic thromboembolism in patients with non-valvular AF. 10/19/10.

- Direct thrombin inhibitor

- Does not requiring monitoring

- Dose:
  - CrCl > 30ml/min - 150mg twice daily
    - CrCl 15-30ml/min – 75mg twice daily
  - CrCl < 30ml/min or dialysis – not recommended
  - Swallow capsules whole.
  - Supply must be kept in bottle
Dabigatran (Pradaxa)

ADVANTAGES
- No monitoring required
- Effective in preventing stroke
- Few drug interactions
- Fast onset

DISADVANTAGES
- Increased risk of GI bleeding
- Accumulation in renal failure
- No antidote
- Difficult to monitor
- Twice daily dosing
- Cost ($3.80 per capsule)
Dabigatran (Pradaxa)

- Warnings/Precautions
  - Renal impairment
  - Hepatic impairment

- Side Effects
  - Dyspepsia
  - GI bleeding
  - Gastritis symptoms
  - Major and minor bleeding
Is it "butt naked" or "buck naked"?